

REMARKS

Claims 1, 5-9, 11-15, 20-25, 27, 29-59 and 61 are being examined and all stand rejected.

In response to the follow-up Office Action, dated 7 October 2003, Applicant has now further amended the previous response by listing claims 16-19 as canceled, by listing claim 60 as canceled and by listing claims 62-68 as canceled, in line with the previous amendment.

As to the Examiner's response to Applicants' earlier arguments, Applicants further respond as follows.

In response to ¶7 of the Office Action (where letters relate to the Office Action):

A) Claims 1 has been amended to remove the language that should have been previously deleted and no longer recites different types of dNTPs.

B) As to claim 50, this claim has been canceled.

C) As to claims 56 and 61, these have been amended so that phrases like "such as" have been removed.

D) Regarding rejection of claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54, 60 and 62 over Lizardi-1 and Lizardi-2, Applicants respond as follows:

Claim 1 recites a method that utilizes at least one dNTP that renders the TS-DNA nuclease dependent. Applicants believe that this limitation avoids this ground of rejection. The Examiner's comment about using only dTTP is not relevant because then there would not be at least one dNTP that renders the product resistant to nucleases. Applicants have

previously claimed such an embodiment (see parent patent 6,323,009 at claims 26 and 28 thereof). Thus, Applicants do not believe that further amendment of this claim, such as to recite "wherein said dNTPs include nuclease-resistant dNTPs" is warranted although Applicants will do so if the Examiner believes that such further amendment will result in increased clarity.

The Examiner further contends that Lizardi-1 suggests use of modified nucleotides to make nuclease-resistant primers and cites to column 10, lines 24-28, as well as column 13, lines 27-31. However, this is a recitation of use of such nucleotides, which were known in the art, for making the replication primers resistant to nuclease activity. Lizardi makes no mention of using such dNTPs to make the TS-DNA product resistant to nucleotides. In fact, the teaching of Lizardi would not suggest such use. Lizardi uses primers that already have nuclease resistant nucleotides in them, which could well be commercially-purchased primers (since Lizardi teaches a method of use and not a product or composition). Lizardi does not teach the use of nuclease-resistant nucleotides in his inventive method, but only as part of a starting material used in his method, which is not the same thing at all.

In fact, Lizardi actually appears to teach away from this use of nuclease-resistant dNTPs. At column 35, lines 2-5, Lizardi describes a procedure that employs a nuclease and mentions the need to protect TS-DNA (the rolling circle product) from degradation. Instead of employing nuclease resistant dNTPs to synthesize the TS-DNA, Lizardi again resorts to primers that contain the nuclease-resistant nucleotides, which then bind to the TS-DNA so that the enzyme (meaning gene 6 exonuclease of phage 7 – see column 34, line 58 and 62-63 – which binds to duplex DNA) the TS-DNA but will eliminate excess open circle probes and gap oligonucleotides. Thus, unlike the teaching of Lizardi, only Applicants herein suggest use of such nuclease resistant dNTPs for direct incorporation into the TS-DNA product as a means of making it nuclease resistant (i.e., when faced with this problem, Applicants' solution is not the one taught by Lizardi).

Applicants believe that this renders the remaining issues moot.

E) As to rejection of claims 8 and 9 over Lizardi-1, Lizardi-2 and Sorge et al., these claims depend from claim 1 and Applicants believe that the recitation of using at least one dNTP that renders the product nuclease resistant also answers this ground of rejection.

F) Regarding rejection of claim 15 over Lizardi-1 and Lizardi-2, Applicants reiterate that the recitation of claim 1 that the dNTPs include nuclease-resistant dNTPs avoids this ground of rejection because claim 15 depends from claim 12 which depends from claim 1.

G) Regarding rejection of claims 32, 41, 46, 47 and 59 over Lizardi-1, Lizardi-2 and Skerra, Applicants contend that the Examiner's reliance on earlier grounds of rejection is mooted by Applicants' argument as to Lizardi's non-teaching of the use of nuclease-resistant dNTPs in forming TS-DNA product, which was only taught by Applicants. All of the cited references, including Skerra, teach use of nuclease-resistant primers and not incorporation of nuclease-resistant dNTPs into TS-DNA. While these claims relate to nuclease-resistant primers, they all indirectly depend from claim 1 and thus include the limitation that the dNTPs include structures that make the resulting TS-DNA resistant to nucleases.

H) Regarding rejection of claims 30, 34 and 43, these claims have been canceled.

I) Regarding rejection of claims 55 and 56 over Lizardi-1, Lizardi-2 and Sorge et al, claim 56 has been further amended for clarity but depends from claim 55, which depends from claim 1 and incorporates all limitations thereof.

J) Regarding rejection of claims 55 and 56 over Lizardi-1 and Lizardi-2, Applicants reiterate the previous response.

Rejection Under 35 U.S.C. 103

Claims 1, 5-7, 11-14, 20-25, 27, 29, 31, 33, 35-40, 42, 44, 45, 48-54 and 61 were rejected as unpatentable under 35 U.S.C. 103(a) over Lizardi (U.S. Pat. No. 5,854,033) and Lizardi (U.S. Pat. No. 6,124,120), referred to as Lizardi-1 and Lizardi-2.

In response, Applicants note that the Examiner has presented a lengthy description of the elements of these various claims that are recited in the Lizardi patents. However, such recitation fails to describe use of dNTPs that make the product nuclease resistant and coupled with use of multiple random primers. The Examiner notes at page 8, lines 5-6, of the Office Action that the primers can be prepared using modified nucleotides to make them (i.e., said primers) nuclease resistant and that these may include phosphorothioate nucleotides but there is no teaching of the use of nuclease resistant modified nucleotides for incorporation into TS-DNA to protect it from nuclease degradation. Only Applicants teach this.

Claim 35 has been amended for clarification.

Claims 8 and 9 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2 in view of Sorge et al, where the latter teaches use of hexamers and octamers as primers. In response, Applicants reiterate their previous arguments regarding use of nuclease-resistant dNTPs, in combination with multiple random primers, to prevent degradation of TS-DNA, which is not taught or suggested in any of the references, either alone or in combination. Applicants believe that any motivation recited as to other aspects of the claims does not render them unpatentable because the elements of Applicants' claim 1 are not inherent in the teachings of the cited references.

Claim 15 was rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2 as already applied to claims 12 and 13. In response, Applicants reiterate their previous arguments regarding the lack of teaching, or even suggesting, use of multiple

random primers along with nuclease-resistant dNTPs, for incorporation into TS-DNA and not just into primers, to achieve nuclease resistance. Thus, claim 15, which depends from claims 12 or 13, which in turn depend from claim 1, incorporates all limitations of claim 1 and is thus patentable over the cited references for the same reasons.

Claims 32, 41, 46, 47 and 59 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2, as applied to claims 1, 38 and 44, and further in view of Skerra et al.

In response, Applicants reiterate their previous argument since these claims all depend, directly or indirectly, from claim 1.

Claims 30, 34 and 43 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2 and further in view of Cummins et al. In response, these claims have been canceled.

Claims 55 and 56 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2 and further in view of Sorge et al. In response, Applicants reiterate their previous argument since these claims all depend, directly or indirectly, from claim 1.

Claims 57 and 58 were rejected under 35 U.S.C. 103(a) as unpatentable over Lizardi-1 and Lizardi-2 as applied to claim 1. In response, Applicants reiterate their previous argument since these claims all depend, directly or indirectly, from claim 1.

If the Examiner believes that a telephone conference with Applicant's agent would facilitate prosecution of this applicant, said agent would be more than ready to discuss this matter further.

The Commissioner is authorized to charge payment of any additional fees required with this communication or credit any overpayment to Deposit Account No. 03-0678.

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